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STEREOSPECIFIC DEXTRORPHAN TOLERANCE IN RATS

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1 Levorphanol was 20 times more potent than dextrorphan in decreasing food-reinforced fixed ratio 15 responding in male Sprague Dawley rats.

2 Chronic dextrorphan (100 mg/kg, i.p.; every 8 h) resulted in the development of dextrorphan tolerance. The dextrorphan dose-effect curve was shifted to the right three fold.

3 In contrast to dextrorphan, nontolerance developed to the effects of levorphanol.

4 These data support the hypothesis that (+)-isomers of opioids produce pharmacologically distinct CNS effects.

Introduction

Dextrorphan is the non-analgesic (+)-isomer of the analgesic opioid, levorphanol. Isbell & Fraser (1953) found that dextrorphan neither substituted for morphine in dependent humans nor did it produce a morphine-like physical dependence when chronically administered to humans. Jacquet, Klee, Rice, Iijima & Minamikawa (1977) have described *in vivo* effects of (+)-opioid isomers which are not blocked by naloxone. Martin & Jasinski (1979) found that chronic dextrorphan administration results in a non-morphine like physical dependence in rhesus monkeys.

Both levorphanol and dextrorphan have been reported to produce decreases in operant behaviour (Woods & Carney, 1978). The chronic administration of the analgesic (−)-isomer of opioids results in the development of a stereoselective tolerance to their behavioural effects (Woods & Carney, 1978). However, no studies have been described in which the (+)-opioid isomer was chronically administered to animals and the subsequent development of tolerance determined.

In this paper we show that under a regimen of chronic injections of dextrorphan, tolerance develops to its effects without any change in sensitivity to levorphanol.

Methods

Six male Sprague Dawley rats were food deprived to 80% of their *ad libitum* feeding weights and trained to bar-press with food reinforcement. Once trained, the response requirement was increased to 15 responses/reinforcement (fixed ratio 15, FR15; Iversen & Iversen, 1975). The 80% deprivation weights were maintained by post-session supplemental feeding. Rats were maintained under a 12 h/12 h light-dark cycle in a 22°C room. Water was freely available. After responding appeared to be stable (no consistent trend for 15 consecutive sessions), the non-tolerant dose-effect curves for levorphanol and dextrorphan were determined. Drugs were injected (i.p.) 15 min before the start of the 30 min session. Drugs were tested in an unsystematic order of doses and no more frequently than every 3 days. The dextrorphan dose-effect curve was determined before testing levorphanol under both the non-tolerant and tolerant condition. Following these determinations, chronic dextrorphan (100 mg/kg) injections were given every 8 h. One of the 3 daily injections was given 15 min before the start of each daily session. After tolerance had developed, doses of dextrorphan or levorphanol were substituted for the 100 mg/kg maintenance dose of dextrorphan. Test doses for determination of dextrorphan tolerance and levorphanol cross-tolerance were administered no more frequently than every 5th day. Drug doses refer to the salt.

Data are expressed as the mean of a single observation in each of the six rats. Differences in dose-effect curves were determined by probit analysis.

Results

Both levorphanol and dextrorphan produced dose-related decreases in rate of responding. Levorphanol was about 15 times more potent than dextrorphan, the ED_{50} for decreasing responding being 2.1 mg/kg for levorphanol and 30 mg/kg for dextrorphan (Figure 1).

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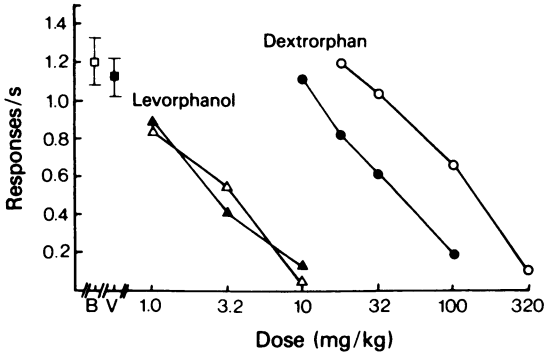

Figure 1 Selective changes in sensitivity to the effects of dextrorphan on food reinforced FR15 responding after chronic injections of 100 mg/kg dextrorphan, i.p., every 8 h. Solid symbols represent the effect of dextrorphan (●) and levorphanol (▲) before chronic dextrorphan. Open symbols represent the effects of dextrorphan (○) and levorphanol (△) during maintenance at 100 mg//kg dextrorphan every 8 h. Each point is the mean of single observations in each of 6 rats. Non-injection baseline (B) and 0.9% saline vehicle (V) data are the group means (± s.e. mean) of 6 observations in each of 6 rats. Probit analysis indicated a significant ($P < 0.05$) shift only for the dextrorphan dose-effect curve and not for levorphanol. See Methods for additional details.

When dextrorphan at 100 mg/kg was administered chronically, tolerance appeared to develop rapidly. A progressive increase in dextrorphan-suppressed responding occurred over the initial 25 sessions of chronic dextrorphan injections. On day 1 of chronic dextrorphan, responding was reduced to 0.18 ± 0.07 (s.e. mean) responses/s. By day 25 of chronic dextrorphan, responding occurred at 0.63 ± 0.06 responses/s. Redetermination of the dose-effect curves provided additional evidence of tolerance development. The dose-effect curve for dextrorphan was shifted to the right three fold in the tolerant rats. In contrast, the levorphanol dose-effect curve was unaffected following chronic dextrorphan injection (Figure 1).

Discussion

The greater potency of levorphanol in suppressing responding, compared with dextrorphan, is similar to that found in previous studies (Woods & Carney, 1978). It is possible that the mechanisms underlying the disruptive effects of the two isomers are different. Martin & Jasinski (1977) have provided *in vivo* evidence for multiple opioid receptor systems which involve at least three different forms. Since tolerance developed to the effects of dextrorphan on operant behaviour and no cross-tolerance to levorphanol could be demonstrated, the possibility exists that there is a population of receptors to which dextrorphan selectively binds and produces its behavioural effects. The demonstration of *in vivo* activity of intracerebrally administered (+)-morphine (Jacquet, *et al.*, 1977), the dextrorphan displacement of methadone from high affinity binding sites in rabbit brain synaptosomes (Ciafolo, 1979) and the results of the present study all suggest the existence of a (+)-isomer opioid receptor system.

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